Function of connexins in the renal circulation

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Connexins form intercellular channels that span two plasma membranes and directly couple the cytoplasm of adjacent cells. This morphological contact enables the exchange of ions, second messengers, and metabolites, which act to regulate several biological functions. This review focuses on the significance of connexins in the renal circulation. Cells of the renal vasculature are coupled and express connexins in a vessel and cell-specific pattern. This finding indicates that renal connexins likely play an important role in renal autoregulatory mechanisms (Bayliss effect, tubuloglomerular feedback) and in the control of vasomotor responses. The described coupling of endothelial and vascular smooth muscle cells in the afferent arterioles may also contribute to the communication of neighboring nephrons, called 'nephron coupling.' Furthermore, deletion of the Cx40 and Cx43 genes results in an altered functional behavior of the renin-producing cells, suggesting involvement of these connexin isoforms in the regulation of renin secretion and synthesis. In addition, this review discusses the role of renal connexin expression in the pathogenesis of hypertension or diabetes.

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CONNEXINS: GENERAL STRUCTURE

Connexins are integral membrane proteins that assemble in large transmembrane channels, named connexons or hemichannels. Gap junctions, which can be investigated by electron microscopy, electrophysiological methods, immunohistochemistry, or dye transfer experiments, are composed of two hemichannels (connexons). These connexons are expressed in the plasma membrane of opposing cells and form functional intercellular channels, which directly link the cytoplasm of two adjacent cells. Each connexon consists of six connexin (Cx) protein subunits that enclose a central aqueous pore. The effective pore diameter varies over a range of 0.8–1.6 nm and is determined by the connexin isoform.[1–3] To date, the connexin gene family comprises of at least 20 different connexin genes in the mouse genome and 21 in the human genome, with significant homology of the respective connexins between human and mouse.[4–6] Members of the connexin family are distinguished from each other by their predicted molecular weights expressed in kilodaltons (for example, Cx40 is 40 kDa).

The single connexin protein is made up of four-membrane-spanning domains with two conserved extracellular loops that are the essential elements of the docking process, one cytoplasmic loop, and cytoplasmic N- and C-terminal regions (Figure 1), which are the most variant portions of the protein.[6,7] Connexins can assemble into homomeric connexons when six identical connexins combine to form the hemichannel. Additionally, they can also form heteromeric channels, consisting of two or more connexin variants. Connexons subsequently combine with identical or different connexons and form homo- or heterotypic gap junctions.[8–10] Heterotypic gap junction channels may be composed of homomeric and/or heteromeric connexons (Figure 1).[11] Thus, an unexpected complexity exists in the composition of gap junctions, whereas not all connexins are compatible to form heteromeric or heterotypic channels.[12,13] The particular combination of connexin isoforms within the channels contributes to the distinct electrical and biochemical properties of the gap junctions.[14] Apart from the isoform composition, channel conductance can be modulated by various factors. The gating properties of gap junctions depend on stimuli such as pH, Ca^{2+}, transmembrane and transjunctional voltage,[15] or protein phosphorylation events that lead to modifications in tyrosine, serine, and threonine residues and have been reported to affect intercellular communication.[16–19] Furthermore, channel conductance can

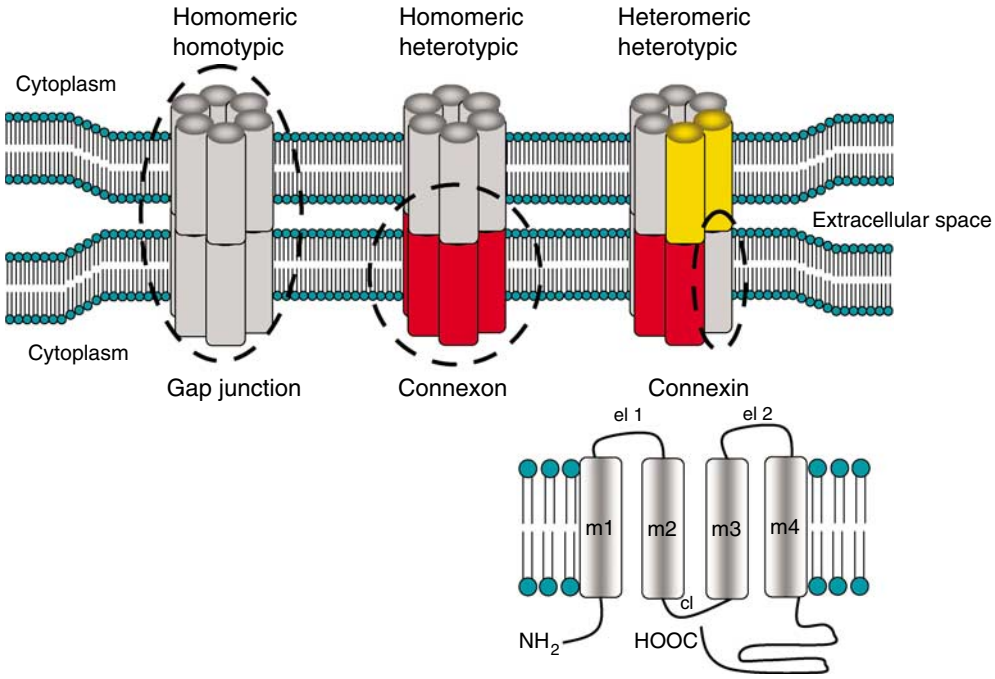

Figure 1 | Connexin structure. Schematic model illustrating assembly of connexins into gap junctions. Six connexin subtypes oligomerize into connexons or hemichannels, which combine into homotypic, heterotypic/homomeric, or heterotypic/heteromeric gap junction channels. The connexin protein creates four membrane domains (m1–m4) with two extracellular loops (el 1 + 2), one cytoplasmic loop (cl), and the N and C termini exposed to the cytoplasm.

be regulated by the number of channels, which is controlled by the up- and downregulation of connexin synthesis, assembly, trafficking, and the rate of degradation.[20,21]

CONNEXINS: SIGNAL TRANSDUCTION

Connexins form gap junctions that allow the diffusional swap of various molecules up to a molecular mass of 1 kDa (for example, ions, second messengers, or metabolites)[8,19,22,23] and present the molecular basis of direct intercellular signaling. The type and number of molecules that spread from cell to cell through gap junctions in a given time period depends on the diameter, size, and charge of molecules in the pore. There is a common agreement that not only monovalent and divalent ions such as sodium, potassium, calcium, and chloride but also uncharged molecules including glucose can pass through most gap junctions. Apart from calcium, other relevant signaling molecules such as cAMP, cGMP, inositol trisphosphate, and ATP can spread from cell to cell through gap junctions.[24–27] It has been demonstrated that connexin isoforms can influence the permeability of gap junctions to signaling molecules. For example, gap junctions composed of Cx43 have a considerably higher permeability to AMP, ADP, and mainly ATP compared to Cx32 channels, although adenosine traverses Cx32 gap junction channels at a 12-fold higher rate.[27] The permeability of gap junctions is subject to regulation. Thus, calcium seems to modulate the passage of molecules through gap junctions, as high or more focal elevations of intracellular Ca^{2+} act to close gap junction channels,[28] whereas lower Ca^{2+} levels exert no effect on gap junctions.

CONNEXINS: GENERAL FUNCTIONS

Except for a few tissues like erythrocytes, thrombocytes, mature skeletal muscle fibers, and spermatozoids, gap junctions are present in all vertebrate cell types.[29] However, the expression of certain connexins is specific relative to tissue and cell type. Cell-to-cell channels are involved in the regulation of several physiological and pathophysiological functions such as cell growth,[30] glandular secretion[31] proliferation and differentiation, developmental processes, tumorigenic processes, and regeneration and so on.[32,33]

Mutations in connexin genes have been associated with a number of human diseases, such as chromosome X-linked Charcot–Marie–Tooth disease,[34] which is caused by mutations in *Cx32*,[35,36] congenital deafness and skin diseases, which have been linked to mutations in human *Cx26*,[37] and congenital cataracts, which are affected by mutations in *Cx50*.[35]

CONNEXINS: SPECIAL FUNCTION

Gap junctions assure the mechanical and electrical coupling of different cell types. Such a role is critical in tissues like the mammalian nervous system, in which gap junctions provide a mode of direct interneuronal communication between adjacent neuronal cells in addition to indirect transmission via chemical synapses,[38–43] and in the heart, where gap junctions permit the rapid cell-to-cell transfer of electrical impulses and guarantee the coordinated contraction of cardiomyocytes.[44–49]

Gap junctions are also present in the vascular system. Communication via gap junctions has been demonstrated to

be an important mechanism in the control of vascular function where they are thought to facilitate communication between cells within the blood vessel wall and coordinate the regulation of vascular tone.[50] Thus, the coupling of vascular smooth muscle cells may be responsible for the synchronous contraction of small blood vessels, whereas junctions between endothelial and vascular smooth muscle cells, the so-called myoendothelial gap junctions (MEGJs), are thought to transmit signals from the endothelium to the underlying smooth muscle cells. Finally, gap junctions between endothelial cells might transport intracellular signals to endothelial cells of upstream arterioles, causing a conducted vasomotor response.[51] The main connexins expressed in vascular cells are Cx37, Cx40, Cx43, and Cx45.[52,53] Vascular connexins, however, show no homogenous expression pattern between different tissues and even between cell types within the same tissue.

In addition to the broad range of human diseases implicated with mutations in connexin genes, numerous studies have been undertaken in animals deficient in different connexins to determine their physiological function. For example, mice with genetic disruptions in vascular connexins show abnormalities in vascular tone and in propagation of vasomotor responses. Thus, *Cx40* knockout mice exhibit hypertension and show impaired conduction of endothelium-dependent vasodilator responses along arterioles,[54,55] which indicates a role of Cx40 not only in the control of blood pressure but also in the propagation of vasodilation. Mice with an endothelium-specific deletion of Cx43 circumventing the neonatal lethality of *Cx43* gene disruption are described as normotensive[54,56] or soft hypotensive.[57] The absence of Cx45 causes vascular malformations during development and blocks the differentiation of smooth muscle cells, resulting in the narrowing of some vessels and early death.[58] Observations obtained from these experiments attest to the physiological significance of connexins or, rather, gap junctions in the development and regulation of vascular function.

The renal vasculature does not only regulate the renal blood flow, but is also involved in the control of glomerular responses, thus making the renal vasculature an interesting system for the examination of vascular gap junctions.

CONNEXINS: LOCALIZATION IN THE RENAL VASCULATURE

The distribution of connexins in the vascular system has been investigated in a series of studies that have detected Cx37, Cx40, Cx43, and Cx45 as the major connexins expressed in the vessel walls. Although connexins are not uniformly expressed in all blood vessels and vary between different species, arterial endothelial cells most notably seem to express Cx37 and Cx40, whereas smooth muscle cells express Cx43 and Cx45. In the following section, the localization of connexins will be described explicitly in the vasculature of the kidney (Table 1).

In large renal vessels (for example, renal, interlobar, and arcuate arteries), the connexin isoforms Cx37, Cx40, and Cx43 were found in the endothelial layer,[59–62] although Cx43 expression is weak and irregular. This finding is consistent with previous studies showing Cx43 in the endothelium of rat aorta or carotid artery,[63,64] but this is in contrast to a recent study in which Cx43 was not found in the mouse aortic endothelium,[65] indicating substantial species and tissue differences. However, information about connexins in the arterial media of large renal vessels currently available from the literature is insufficient and confusing. Although it is generally described for major arteries that smooth muscle cells express Cx37, Cx40, Cx43, and Cx45,[60] the exact connexin expression in the media of larger renal arteries is still unclear. Currently, there is immunohistochemical evidence that Cx37 and Cx43 are expressed in the media of large renal arteries.[61,66]

Table 1 | Summarization of the connexin distribution in renal arteries of the mouse

	Large renal arteries		Renal arterioles		
	Endothelium	Media	Endothelium	Media	Renin-producing cells
Cx37	++	+	++	–	+
Cx40	+++	–	+++	–	+++
Cx43	+	+	+	+	–

Much more information is available from the distribution of connexins in renal arterioles. The endothelial cells express Cx37 and Cx40 and weakly express Cx43,[59–61,67] which is largely consistent with different species and agrees with the pattern of extrarenal arterioles.[53,54,68,69] In the media of afferent arterioles, connexin subtypes Cx37 and Cx43 are expressed, whereas Cx37 was only found in the preglomerular vessels of mice,[61] but not in the rat kidney.[70] Investigations of rat and human kidneys show either no expression of Cx43 in the smooth muscle cells of afferent arterioles[67,70,71] or only weak expression in the media of the afferent arterioles.[59] However, investigating connexins in the afferent arterioles in more detail reveals an interesting heterogenous expression pattern of connexins along the arterioles. Although the proximal portions of the afferent arterioles show typical Cx40, Cx37, and also weak Cx43 expression in the endothelium, no gap junctional coupling through these connexin isoforms can be detected in the distal parts of these vessels, in which Cx40 can be found in the smooth muscle cell layer.[70] Consistent with this result, remarkable Cx40 immunoreactivity was observed not only in the renin-producing cells of the juxtaglomerular apparatus (JGA), considered to be modified smooth muscle cells, but also in extraglomerular and intraglomerular mesangial cells.[59–62,67] Cx37 is expressed in renin-producing cells as well as in the extraglomerular mesangium and mesangial cells near the vascular pole.[61] In contrast to the afferent arterioles, only Cx43 was detected in the endothelial cells of efferent arterioles and there was no connexin expression in the media, suggesting extensive coupling of the cells in the preglomerular vasculature but not in postglomerular vessels.[61]

In summary, cells in the wall of the large renal vessel appear to have a relatively normal connexin expression pattern, suggesting that connexins exert physiological functions, which correspond to their role in the general vascular system. In contrast, connexin expression, especially in the distal part of the afferent arterioles, completely differs from the common pattern by striking extensive but heterogeneous Cx40 expression, which may contribute to the regulation of glomerular function or renal endocrine function.

CXS: ROLE IN RENAL HEMODYNAMICS

The control of renal blood flow is determined by sympathetic nerves, by endothelial function, and by autoregulatory mechanisms. The latter comprise mainly a myogenic component, commonly known as the Bayliss mechanism and the tubuloglomerular feedback (TGF, see below). This myogenic reaction has been demonstrated in a previous study, where preparations of blood-perfused juxtamedullary nephrons abrupt increases in perfusion pressure result in the vasoconstriction of afferent arterioles in a spatially organized manner.[72] As it is assumed that the myogenic response is activated by a depolarization that opens voltage-dependent channels and leads to an inward Ca^{2+} current, one may hypothesize that the electrotonic diffusion of Ca^{2+} may occur throughout gap junctions connecting the medial layer.[73] In fact, several studies in the literature have verified the electrical coupling of smooth muscle cells in afferent arterioles using electrophysiological methods.[74,75] This assumption was further supported by studies conducted in neuronal arteries, in which the uncoupling of gap junctions by the inhibitor α-glycrrhentinic acid significantly impaired myogenic vasoconstriction.[76] However, there are no studies detailing the involvement of connexin proteins in mediating the Bayliss effect.

The contractile status of smooth muscle cells can be further regulated by the endothelial release of vasoactive substances, so-called autocoids, which include nitric oxide (NO), prostaglandins, or the endothelium-derived hyperpolarizing factor.[77,78] It is conceivable that the relaxing action of autocoids on smooth muscle cells is mediated via MEGJs, which couples endothelium cells directly with the media layer. MEGJs have been described in some extrarenal vascular tissues, mostly in smaller arterioles, to be involved in vasotonus control.[79–81] In renal vessels, Cx40-containing gap junctions are present in endothelial and renin-producing cells,[67] although no evidence for MEGJs among normal smooth muscle and endothelial cells exists. Although NO or PGI_2 presumably diffuse from the endothelium to the smooth muscle cells, subsequent relaxation is not affected by gap junction blockers.[82] Endothelium-derived hyperpolarizing factor activity, in contrast, seems to be dependent on gap junctional coupling.[83] Information about certain connexins involved in mediating the vasomotor responses is limited and only available from studies conducted on extrarenal tissues such as rat mesenteric and basilar arteries, in which MEGJs are described to be composed of Cx37 and Cx40.[84,85] Furthermore, in human subcutaneous arterioles, endothelium-derived hyperpolarizing factor-induced vasodilatation was shown to be dependent on Cx43 using the mimetic peptide ^{40}Gap26.[69]

In the microcirculatory system, the vasomotor responses can spread along the vessel wall to facilitate dilatation or constriction of upstream arterioles according to blood flow requirements. The propagation of vasodilatation or vasoconstriction is linked to an electric conduction of a hyperpolarizing or depolarizing current, which is known to flow through gap junctions[86] and couples cells of either the endothelium or the smooth muscle of arterioles. Conduction of depolarizing currents has already been shown in renal afferent arterioles in rats, where the microapplication of KCl causes the spread of a local vasoconstriction over a distance up to 1500 μm[87,88] to produce a sufficient increase in afferent arteriolar resistance. The conduction of vasodilatation has also been shown to be dependent on intercellular coupling. In skeletal muscle arterioles of mice deficient for *Cx40*, conduction of vasodilatation was markedly impaired,[54,89] suggesting that the vasodilatory response requires cell coupling via Cx40. The question remains whether conduction of the vasomotor responses is conducted along the endothelium or along the media of the arterioles. To explore this issue, investigations in mice where the continuity either in endothelium or smooth muscle cells was interrupted show that vasodilatation is conducted along the endothelium, whereas vasoconstriction is conducted in the media.[79,90] This assumption fits well with the attenuated conductance of vasodilatation in mice lacking *Cx40*, which is known to be the predominant endothelial connexin protein.[54] The role of specific connexins in the regulation of the vasomotor responses in the kidney is currently unknown and requires further investigation.

CXS: ROLE IN TGF SIGNALING

The glomerular filtration rate of the kidney is controlled via the TGF mechanism. For this sophisticated feedback loop, a specialized site of the nephron (the macula densa) contacts its own afferent arteriole in the JGA. The macula densa cells sense increasing sodium chloride concentrations in the tubule lumen and send vasoconstrictor signals to smooth muscle cells inside the wall of the afferent arteriole to regulate the preglomerular diameter and thereby decrease the glomerular filtration of the respective nephron.[91,92] This process requires transfer of the vasoconstrictor signal from macula densa cells via the strategically positioned extraglomerular mesangial cells to the smooth muscle cells in the afferent arteriole.[93–95] As shown in a previous study, cells of the JGA, except those of the macula densa,[96] are coupled via gap junctions[97,98] to establish a pathway for the transmission of the vasoconstrictor signal. Indeed, the importance of gap junctions within the JGA and their role in TGF was recently presented in a study where damaging mesangial cells with a Thy 1-1 antibody and the disruption of gap junctions by heptanol led to the elimination of TGF.[99] Heptanol treatment does not compromise the function of JGA cells. A study by

Ren *et al.*[99] was unable to elucidate whether TGF requires coupling between the mesangial cells, an intercellular link between mesangial cells and smooth muscle cells, or a continuous connection between these different cell types.[100] Information about the connexin subtypes that determine the TGF has not been elucidated, although numerous findings suggest that Cx40 is the main junctional protein in the JGA.[60,61,67,70] In agreement with these investigations, we recently observed that the genetic disruption of the *Cx40* gene in mice is associated with increased interstitial spaces and the failure of intercellular coupling between extraglomerular mesangial cells.[101] To gain greater insight into the function of certain connexins such as Cx40 in TGF signaling, additional experiments will be necessary to study whether the absence of connexin proteins allows the transmission of macula densa signals to the afferent arteriole.

There is accumulating evidence that ATP is released from macula densa cells in response to increasing sodium chloride concentration in the tubule lumen.[102–104] As there is no cell coupling between macula densa cells and mesangial cells, it appears that macula densa cells release ATP at their basolateral membrane probably through connexin hemichannels, which may provide a pathway for the release of paracrine signals.[105–107] The binding of ATP to P_2X or P_2Y receptors, which are abundantly expressed in cells of the JGA,[108–111] triggers a calcium wave that spreads from the macula densa via the extraglomerular mesangium toward the afferent arterioles.[95] Interestingly, the uncoupling of gap junctions by gap junction uncoupling agents, α-glycrrhentinic acid or heptanol, abrogates increases in intracellular calcium and the spreading of the calcium wave,[95,112] suggesting an essential role of cell coupling in the TGF mechanism.

In summary, although there is accumulating evidence that gap junctions play a role in mediating TGF signaling, detailed information about the localization of participating gap junctions in the JGA or involved connexin subtypes is still lacking.

More studies are necessary to define the exact role of connexins in the regulation of the TGF mechanism.

CXS: ROLE FOR NEPHRON COUPLING

The TGF controls regular oscillations of hydrostatic pressure in the glomerular capillaries. The capillary pressure of two neighboring glomeruli often oscillates synchronously.[87,113,114] As experimentation of the TGF response at a defined glomerulus also leads to an almost simultaneous TGF response in a neighboring glomerulus, it is obvious that two neighboring glomeruli communicate with each other, a phenomenon that has been termed 'nephron coupling.' The structural basis for this nephron coupling is bi- or trifurcated endings of afferent arterioles. The nephron coupling mechanism involves retrograde signal propagation from one vascular pole to the branching sites followed by orthograde propagation of the signal into the other branches.[72] The signal itself must influence the tone of the afferent arterioles, in particular, at the entrance into the glomerulus. The signal is conducted along the walls of the afferent arterioles through gap junctions. In principle, signal conduction could also occur along the endothelial or the smooth muscle cell layers. From the available data, it is not yet possible to attribute nephron coupling to endothelial or smooth muscle cell gap junctions. Knockout mice should provide a powerful tool that could aid in addressing this issue. For example, endothelial conduction could be expected to be impaired in *Cx40*-deficient mice, whereas mice with a vsmc-specific disruption of the respective connexin genes should show altered conduction along the media layer. The nature of the propagated signal will likely be characterized in future experiments. The simplest explanation is that changes in membrane potential are propagated from one afferent arteriole to another.[87] As the smooth muscle cells of afferent arterioles contain calcium channels,[115,116] changes in the membrane potential would be rapidly transformed into changes in vessel tone. In this context, Wagner *et al.*[87] have demonstrated that vasoconstriction induced at the distal end of a certain afferent arteriole by KCl application was conducted in the cortical radial artery and adjacent afferent arterioles in the rat kidney. Interestingly, the conduction of these vasomotor responses was much greater in spontaneous hypertensive rats, indicating strengthening of internephron coupling in the hypertensive state. One may hypothesize that the known enhanced Cx40 and Cx43 expression during hypertension (see section below) may improve the intercellular coupling within the vessel wall, thus causing the intensified conduction of neighboring nephrons in spontaneous hypertensive rats. However, this issue is still unclear and requires further investigation to determine whether the hypertension-induced elevation of connexins primarily affects endothelium coupling or junctional communication between smooth muscle cells.

CXS: REGULATION OF RENIN SYNTHESIS AND SECRETION

The JGA represents a multilayer morphological structure, which comprises of several cell types in a very small kidney compartment. It has been known that these cells are strongly coupled via gap junctions. Morphological evidence has been corroborated by functional data indicating strong electrical coupling of renin-secreting cells.[74,75,117] Within the JGA, renin-producing cells form numerous gap junctions between renin-producing cells themselves as well as between renin-producing cells and the adjacent endothelial or extraglomerular mesangial cells.[97,118] The predominant isoform of connexins in renin-producing cells is Cx40 (Figure 2), which is expressed in high density in these cells.[60,63,66] The expression pattern of Cx40 is remarkable. Within the vasculature, Cx40 is expressed almost exclusively in the endothelium. For renin-producing cells that are known to replace vascular smooth muscle cells in the media of distal portions of the afferent arterioles, one would expect that they do not express connexins, which are typical for the endothelium, but specifically connexin subtypes including

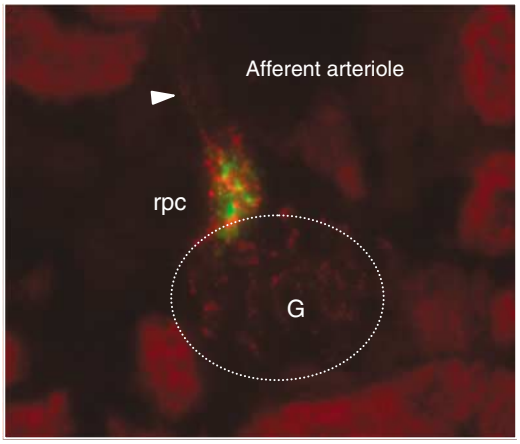

Figure 2 | Cx40 expression in the afferent arteriole. Immunofluorescence analysis of cryostat sections of mouse kidneys shows Cx40 expression in the endothelium of the afferent arteriole (indicated by arrows) and in renin-producing cells (rpc). Green staining for renin; red staining for Cx40.

Cx43, which are normally found in vascular smooth muscle cells. Interestingly, juxtaglomerular renin-producing cells do not express Cx43.[59,67,70] Although the functional relevance of the striking cell coupling in the JGA has not been extensively studied, one may hypothesize that Cx40-mediated contact in renin-producing cells with either the endothelium or mesangial cells provides an ideal pathway for signals involved in controlling the activity of the renin system. Synthesis and secretion of renin are essentially controlled by circulating angiotensin II levels, the sodium chloride concentration passing the macula densa, and the classic negative feedback loops such as the hydrostatic pressure within the vessel. Most recently, the role of Cx40 gap junctions in the transmission of inhibitory signals has been addressed in studies using the *Cx40* knockout model.[62,119] The classic approach to investigate the influence of blood pressure on renin secretion is the experimental unilateral renal artery stenosis, which led to an increased renin secretion in the hypoperfused kidney causing hypertension and decreased secretion in the contralateral intact kidney. Performing this maneuver in *Cx40*-deficient mice did not lead to an increase in blood pressure and plasma renin concentration and did not promote the expected increased renin secretion in the hypoperfused kidney.[62,119]

Investigations of the inhibitory action of Ang II on the renin system led to similar results. This has been shown by *in vivo* experiments in which diminished circulating Ang II levels resulting from ACE inhibition led to a clearly reduced stimulation of renin secretion and renin synthesis in Cx40−/− mice.[62,119] Finally, it could be shown that the deficiency of *Cx40* interrupts the inhibitory macula densa signaling of renin-producing cells. Thus, the application of loop diuretics normally stimulates the activity of the renin system in wild-type mice, whereas this stimulating effect is markedly attenuated in Cx40 knockout mice.[101] These findings indicate that the classic feedback loops, which involve intrarenal blood pressure, Ang II, or salt load rely on cell-to-cell transmission of respective inhibitory signals of renin-producing cells and are disturbed in the absence of Cx40.

Interestingly, mice where *Cx43* (normally expressed in rare endothelial cells and smooth muscle cells in afferent arterioles,[61,66,67,70,119] but not in renin-producing cells) is replaced by *Cx32* (Cx43ki32) displayed markedly reduced renin secretion and failure of hypertension in the model of unilateral renal stenosis.[120] These findings indicate that intercellular communication via Cx40 expressed by renin-producing cells, and also via Cx43 located in endothelial cells, is required for control of the renin system. How the disruption of *Cx40* or *Cx43* genes can exert such characteristic changes in the activity of the renin system is yet unknown and requires further investigation. One could speculate that the overlapping defects in the control of the renin system seen by replacement of *Cx43* or by the deletion of *Cx40* could support a functional link of Cx40 and Cx43 signaling mechanism. As both isoforms do not appear to be compatible to form heterotypic channels,[121] one could imagine that due to the spatial vicinity of the cells within the JGA, transmission of humoral factors by paracrine signaling may also play a certain role for the control of the renin system.

CXS: MODULATION OF THEIR EXPRESSION IN THE KIDNEY

Connexins have been described in numerous studies to be involved in the development of vascular pathophysiology in that they modulate their expression levels.[50,54,122,123]

For example, diabetes induction by intraperitoneal injections of streptozotocin causes a modified expression of Cx40 and Cx43 in the renal vasculature of C57Bl/6 mice. In controls, Cx40 is expressed in the endothelium of the afferent arterioles and appears in the media only in the terminal part of these vessels. However, Cx43 was detected in endothelial cells of the efferent arterioles as described above. In diabetes, increased Cx40 expression was observed in vascular smooth muscle cells along the afferent arterioles and inside the glomerulus. However, Cx43 staining in the endothelium along the efferent arteriole decreased considerably, indicating that during diabetes the intercellular communication via gap junction is enhanced in the preglomerular vasculature, but concurrently abrogated in the postglomerular parts.[61,124] These observations are supported by an *in vitro* study that demonstrates the downregulation of Cx43 in mesangial cells exposed to a high glucose medium.[125] In addition to the altered connexin expression in diabetes, the availability of NO increases with this disease. Zhang *et al.*[124] investigated the possible role of NO on the changes in connexin expression. In a very elegant experimental strategy, connexin expression was studied in mice with overexpression or deletion of endothelial NO synthase activity. Interestingly, mice overexpressing endothelial NO synthase showed changes in Cx40 and Cx43 expressions similar to the modified connexin expression in wild-type mice during diabetes. Basal Cx40 and Cx43 expressions in endothelial NO synthase knockout mice do not differ from wild-type mice, and

the induction of diabetes produces no alteration of connexins either in preglomerular or postglomerular parts of the renal vasculature. This leads to the assumption that NO, which is regulated by endothelial NO synthase activity, may contribute to the changes in connexin expression during diabetes. This is in contrast to a subsequent *in vitro* study that also investigated the involvement of NO in the control of gap junctions and Cx43 expression, but exhibited NO as a potent Cx43 stimulator.[126]

Modifications of connexins in the kidney have been further described in studies interested in the pathogenesis of hypertension. One of theses studies investigated the effects of renovascular hypertension induced by unilateral renal artery clipping. As shown by molecular biological analysis, experimentally induced high blood pressure leads to an increase in Cx40 mRNA and protein in the clipped and non-clipped kidneys, whereas Cx43 was only increased in the non-clipped kidney. Immunohistochemical analysis revealed that the elevation of Cx40 protein was due to its enhanced expression in renin-producing cells in the wall of afferent arterioles.[67] Similarly, Cx43 expression is also affected by hypertension in the aortic wall. Independent of the generating mechanism for hypertension, Cx43 expression is markedly increased in different hypertensive models such as the 2K1C, Doca-salt, or L-NAME (N_{ω}-nitro-L-arginine methyl ester hydrochloride) model, which suggests that mechanical forces induced by blood pressure elevation mainly regulate Cx43 expression.[67,127]

In summary, connexins appear to play an important role in the development of vascular diseases. Apparently, the modified cell-to-cell communication between vascular cells disturbs the regulation of normal vascular function causing the pathogenesis of diabetic nephropathy or hypertension, for example.

CXS IN RENAL VASCULATURE: CONCLUSIONS

As there is only limited data to document the function of connexins in the renal vascular system, previous sections have provided support for more possible roles of connexins in the regulation of renal vascular hemodynamics, TGF signaling, nephron coupling, or the renin system. One could infer that if connexins play such a critical role in maintaining renal circulatory function, they are potential molecular targets for the pathogenesis of renal vascular disease. However, it must be stressed that there is presently too little information regarding a direct role of connexins in vascular disease. Interestingly, a polymorphism within the Cx40 promoter has been shown to be associated with increased risk of hypertension in men.[128] Thus, it remains to be elucidated whether changes of renal connexin expression account for genesis of vascular disease in humans. Given this background, it seems to be a very interesting field for additional research.

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